REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance. The present amendment is being made to facilitate prosecution of the application.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 25-47 are currently pending. Claims 1-24 have been canceled without prejudice or disclaimer of subject matter. Claims 25 and 40 are independent. Claims 25, 26, 35, 36, 40 and 41 are hereby amended. Support for this amendment is provided though out the Specification, as filed, and specifically at pages 7 and 11. No new matter has been added. Changes to claims are not made for the purpose of patentability within the meaning of 35 U.S.C. §101, §102, §103, or §112. Rather, these changes are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. 35 U.S.C. §112, SECOND PARAGRAPH, REJECTIONS

In the Final Office Action, claims 25-47 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The amendments to the claims, without prejudice, render the rejection moot.

Consequently, reconsideration and withdrawal of the Section 112, second paragraph, rejections are respectfully requested.

III. 35 U.S.C. §103 REJECTIONS

Claims 25-31 and 33-47 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pompe et al. (AR) in view of U.S. Patent No. 5,560,960 to Singh et al. and Richter et al. (AQ). Claim 32 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pompe et al. (AR) in view of Singh et al. and Richter et al. (AQ) and further in view of U.S. Patent No. 5,670,680 to Newman et al.

Independent claim 25, as amended, recites, *inter alia*:

> "...**removing any non-conjugated metal complexes and/or non-conjugated by-products**; reacting the metal complex-nucleic acid conjugate with a reducing agent to produce a metal nanoparticle-nucleic acid composite, wherein the metal complex-nucleic acid conjugate is formed by the specific metalation of bases of the nucleic acid or by binding of said nucleic acid specific metal complex through **an interactive group**..." (emphasis added)

Applicants submit that the combination of Pompe, Singh, and Richter, taken alone or in combination, does not disclose or suggest the above-identified features of claim 25. Specifically, Applicants note that none of Pompe, Singh, or Richter disclose or suggest the step of "removing any non-conjugated metal complexes and/or non-conjugated by-products," as recited in claim 25.

Therefore, independent claim 25 is believed to be patentable.

For reasons similar to or somewhat similar to those described above with regard to independent claim 25, amended independent claim 40 is also patentable.

As understood by Applicants, Dressick *et al.* (1994) *J. Electrochem. Soc.* 141, 210-220, Page 213, (cited in an Information Disclosure Statement submitted herewith) relates to "[t]he chemistry of simple Pd(II) salts (e g., tetrahalo complexes such as $PdCl_4^2$) in aqueous solution is dominated by hydrolysis of the metal ion above pH of approximately 2. The hydrolysis rate increases rapidly with pH and precipitation of Pd(II) as a complex oxobridged polymer eventually occurs."

Applicants submit that it would be expected that the behaviors of palladium acetate and palladium chloride to be similar since both acetate (a carboxylate) and chloride (a halide) are examples of labile ligands, as explained in the patent application.

Thus, as understood by Applicants, the $Pd2^+$ ion is likely to hydrolyze when the palladium acetate salt is added to distilled water, leading to the formation of polymeric, oxo-bridged clusters of Pd(II). Applicants submit that, according to the Merck Index [Twelfth Edition, entry number 7123], palladium acetate is *insoluble in water.*

As understood by Applicants, Richter *et al.* (2000) *Adv. Mater.* 12, 507-510 Pace 510 relates to "[t]he Pd acetate solution was prepared by dissolving 10 mg of l'd$(CH_3COO)_2$ in 1 ml of distilled water and then placing it in an ultrasonic bath of 2 min. Afterwards it was centrifuged for 5 min at 2000g to obtain a saturated solution and settle all unresolved particles. The Pd acetate solution was mixed for 2 h with an equal amount of DNA solution (DNA, New England Biolabs, 0.005 mg/ml in 10mM Tris [tris(hydroxymethyl)aminomethane] buffer)."

This procedure is similar to the one reported on page 1090 of Pompe *et al.* (1999), but a centrifugation step has been added to "settle all unresolved particles" in the palladium acetate solution.

Applicants submit palladium acetate in water does not simply contain Pd^{2+} ions or the $Pd(CH_3COO)_2$ complex in solution, but instead it is a colloidal suspension containing polymeric clusters of oxygen-bridged Pd^{2+} ions of undefined composition, size, and charge.

Applicants note, in regard to the disclosure content of Pompe and Richter with respect to the sequence of steps and the use of metal complexes in the already known metallization methods, the Examiner argues that the direct binding of a metal complex to nucleic acids is already suggested by Pompe, as Pompe discloses "*binding cis-diamminedichloroplatinum to DNA, and suggests that metal of the resulting conjugate can act as a nucleation center for the growth of metal clusters*" (p. 7-10 and 11 of the Final Office Action).

Applicants submit that Pompe does not disclose the direct binding of cis-diamminedichloroplatinum to DNA, as the concrete metallization method is not disclosed. Pompe describes that they performed molecular dynamics investigations on the mechanisms of cluster formation in the presence of DNA and suggested that Pt (II) and Pd(II) complexes attached to the DNA can act as nucleation centers. However, the specific metallization method, the steps of said method is not taught. It is not disclosed whether the binding of the metal complex to the DNA was direct or if the DNA was pre-treated. Therefore, the direct binding of a metal complex to the nucleic acid is not disclosed.

Furthermore, Applicants submit $Pd(CH_3COO)_2$ in solution is not a metal complex in terms of the invention. The metal complexes in the present invention that bind to nucleic acid via "metalation" (i.e., direct ("covalent")) bonding between the metal center and a site on the nucleic acid) all contain two kinds of ligands coordinated to the metal ion: ligands that are relatively inert towards replacement ("non-labile") and ligands that are relatively reactive towards replacement ("labile"). $Pd(CH_3COO)_2$ contains only one kind of ligand acetate, which is a type

of carboxylate ligand and therefore classified as "labile" according to our disclosure. The labile nature of the acetate ligand(s) in $Pd(CH_3COO)_2$ makes the complex susceptible to hydrolysis by water, resulting in the formation of polymeric species (clusters or colloidal particles) containing multiple Pd^{2+} ions of ill-defined nature. Such clusters may be positively charged and thereby may bind to DNA via electrostatic interactions with the phosphate backbone. In any case, such clusters are not known to bind to nucleic acids by "metalation".

Applicants submit that Pompe discloses that it "*is well known from a large amount of investigations in the past decades that Pt(II) and Pd(II) complexes attach to the DNA bases and lead to very stable monofunctional and bifunctional adducts [31]*". Nevertheless, these examples fall within the class of metal complexes that bind to nucleic acids by "metalation", i.e., direct ("covalent") bonding between a metal atom and a site on the nucleic acid, especially the N-7 atoms of the purine nucleotides (G and A). Although many such examples were known at the time of the present invention, in no case was it demonstrated that the metal complexes bound in this manner could be reduced to form metal nanoparticle-nucleic acid composites.

Furthermore, Applicants submit that it is known from Pompe that Pt(II) and Pd(II) complexes can act as nucleation centers for the growth of metal clusters. Nevertheless, the specific feature to use metal complexes for metallating DNA is that Pompe did not demonstrate that Pt(II) or Pd(II) complexes bound to DNA can act as nucleation centers for the growth of metal clusters (or nanoparticles), unless one regards unpublished, preliminary theoretical results as a suitable demonstration (Ref. 33 of Pompe *et al.* (1999)). As already discussed above, treatment of DNA with $Pd(CH_3COO)_2$ most likely involves clusters and not a distinct complex of Pd^{2+}, so the mechanism of binding is unclear. The specific features to use metal complexes for metalating DNA is foremost the *presence of a DNA-specific binding group*, which may be the

metal center itself ("metalation" or "'covalent'" bonding) or a binding group attached to the metal center via a "non-labile" ligand in the metal complex.

Applicants note that the term "metalation" has more than one meaning as well as more than one spelling ("metalation"). In the medical field, it usually refers to the "covalent" binding of a metal ion to a specific site on a biomolecule, such as a thiol group on a protein or the N-7 atom of a purine base of a nucleic acid. In the electronics field, metalation generally refers to plating (electroplating or electroless plating). However, the plating processes are also referred to as "metallization" (or "metalization"). To avoid confusion, Applicants submit that the term "metalation" applies to binding of a metal ion (or complex) to a biomolecule and use of the term "metallization" applies to the electroless plating process.

As understood by Applicants, Richter discloses activation of the DNA with Pd acetate (p. 510, first paragraph), normally, in this context activation would refer to making the DNA active as a template towards the electroless plating (metallization) process, i.e., the DNA is made catalytic towards electroless metal deposition by the presence of Pd nanoparticles. However, since Richter is referring to the first step only, it is not clear what they mean by "activated".

Electroless metal deposition by the use of salt solutions of a catalytic metal seems to be disclosed, for example, by Singh. (A catalytic metal is one that is active during electroless plating. Commercially, Pd is the most commonly used catalytic metal, perhaps because it is the most active. The metal complexes of our invention also contain catalytic metals (Pd, Pt, Rh, etc.)). Nevertheless, the only catalytic metal complex described by Singh is $Pd(NH_3)_4Cl_2$. This palladium salt is known as tetraaminepalladium(II) chloride, whose formula may be better written as $[Pd(NH_3)_4]Cl_2$ to emphasize the fact that the four ammonia groups are the ligands coordinated to the Pd^{2+} ion, while the two chlorine atoms are chloride (Cl^-) counterions. Since

the ammonia groups are relatively inert towards substitution ("non-labile"), $Pd(NH_3)_4Cl_2$ should be inactive with respect to metalation of nucleic acids. i.e., it should not form a metal complex-nucleic acid conjugate. Although the complex $[Pd(NH_3)_4]^{2+}$ would bind to DNA electrostatically, it would also be removed by cation exchange. Therefore, if DNA were treated with a solution of $Pd(NH_3)_4Cl_2$ and then subjected to cation exchange to remove non-conjugated metal complex, the subsequent addition of reducing agent would not be expected to produce a metal nanoparticle-nucleic acid composite.

Further, Applicants submit that Office Action incorrectly stated that Pompe also discloses a method binding the metal complex to DNA before reducing it, because the palladium acetate complex decomposed by hydrolysis before the "Pd acetate solution" was mixed with the DNA solution.

Furthermore, Applicants note, in regard to the disclosure content of Pompe and Richter with respect to the diameter of the produced clusters, that the Examiner is of the opinion that the clusters of Richter are of 1-5 nm in width. However, as understood by Applicants, Richter does not disclose formation of clusters of 1-5 nm diameters. The cited passage is directed to a *wish*, it is merely disclosed that "*aligned clusters of 1-5 nm diameter **would** allow investigations on single electron tunneling at room temperature*" (p. 508, left column, fourth paragraph of said document; emphasis added).

Thus, the requirements for an investigation on single electron tunneling are disclosed, but not the diameter of produced clusters. However, the produced clusters have a diameter of 3-5 nm (p. 508. right column, second paragraph).

So, Applicants submit, it would have been a wish of Richter to produce clusters not thicker than the DNA. However, there is no prior art teaching about a method for producing

such metal clusters. Therefore, Applicants submit that a person skilled in the art would not able to produce said clusters, and that the solution of this problem is taught for the first time by the present invention. According to Pompe it was "*well known from a large amount of investigations in the past decades that Pt(II) and Pd(II) complexes (in particular cis-diamminedichloroplatinum, or cisplatin) attach to DNA bases and lead to very stable monofunctional and bifunctional adducts*" (p. 1090, left column, third paragraph of said article) Although the use of metal complexes for metallization of DNA seems to be well known, the long-felt need to obtain metallized DNA with a diameter not thicker than DNA was not solved. Thus, Applicants submit, that the present invention solves a technical problem which workers in the art have been attempting to solve for a long time.

Applicants note that the Office Action argues Pompe and Richter can control the size of clusters, namely by controlling the time of metallization. As stated above, the clusters of Richter can be 3-5 nm in width after a few seconds of Pd growth on the DNA; however, *the clusters, with a diameter of 3-5 nm, remain separated after 1 min quasi-continuous coverage is achieved, with cluster aggregates 20 nm in size*. (p. 508, right column. second paragraph). Thus. metallized DNA of 3-5 nm can only be obtained in a very early stage of the metallization process and as a result the formation of clusters is separated, in contrast to the particles obtained by the inventive method. Applicants submit that this method, therefore, has several disadvantages over the claimed method:

a) The handling seems to be problematic to stop the reaction exactly at the time-point the clusters are 3-5 nm in width. The reaction has to be stopped shortly after the start of the reaction. The person handling this

reaction has to be very quick. Moreover, this method would be not useful in the practice of production of large amounts of metallized DNA,

b) After a few seconds the DNA is only discontinuously covered by the cluster aggregates. To achieve a continuous coverage one has to extend the metallization time. However, in that case the cluster aggregates would be 20 nm in, width, thus 20 times thicker than the DNA.

As understood by Applicants, the nanoparticles of Richter are not 1-5 nm in width: see above, thus, the clusters of Richter do not encompass sizes smaller than 3 nm. Therefore, the claimed metal nanoparticles are smaller than the nanoparticles disclosed by Richter.

Furthermore, Applicants note, in regard to the step of removing any non-conjugated metal complexes and/or non-conjugated by-products, that the Office Action stated that "*the objective of Pompe et al. is to obtain metal clusters on the DNA and not at other places, and to accomplish this one would obviously have to remove none attached metal complex before electroless metallization*" (p. 6, lines 7-11 of the Final Office Action). Applicants submit that the Examiner is correct to say that the objective of Pompe is to obtain metal clusters on the DNA and not at other places. But it seems it is not correct that one would obviously have to remove non-attached metal complexes before electroless metallization to accomplish this. As understood by Applicants, Pompe does not introduce such a removing-step in the metallization method, although it was an object to obtain clusters not thicker than the DNA and to obtain clusters only, on the DNA.

Applicants further note that the Examiner seems to believe that the step of separating the byproducts as claimed does not have to function to produce smaller clusters and a larger surface

energy. However, by preventing the non-attached metal complex from forming metal particles smaller particles can be produced. This step is not for preventing the unreacted reactants from interfering with subsequent steps of reacting.

Applicants submit that having more metal complex present during the reduction step will lead to more reduced metal. Whether more metal means that there will be more particles or that the average size of particles will be larger is not a question that can be answered, although both possibilities are likely. The question of where the metal particles are located seems to be just as important, if not more so. If metal complexes are free in the solution phase or bound electrostatically to the phosphate backbone, it seems likely that these will lead to the formation of additional metal particles that are less protected by the nucleic acid and therefore harder to control both in size and location. Insuring that all the metal complexes are part of the nucleic acid conjugate provides greater control over both the size and location of the metal particles by providing a surface-stabilizing environment.

Applicants note that the Examiner's position appears to be that all the skilled reader of Pompe and Singh had to do to solve the problem underlying the invention would have been to combine the teachings of those two documents. However, Applicants submit that the skilled person faced with the stated technical problem and considering the teachings of those two documents and common general knowledge would not modify the metallization process of Pompe by introducing the removing step to control the sizes of the clusters. The principle underlying the teachings of Singh is indeed to remove metal from the exterior of vesicles to prevent metal particles from being formed on the vesicles exterior surface, but not to control the size of the vesicles by this removing step. Singh provides no practical guidance for controlling the sizes of particle formation. Therefore, Applicants submit that the skilled person would not

consider the teachings of Singh to control the sizes of cluster-formation of nanoparticles on the DNA. This is the teaching of the present invention. By the introduction of this step into the metallization process, smaller clusters can be obtained, which is not obvious.

Applicants further submit, in regard to the interactions between metal complexes and nucleic acids, that according to the Office Action, the present claims do not exclude ionic interactions from forming clusters. Applicants submit that the claim requires that the metal complex-nucleic acid conjugate is formed by the specific metalation of bases of the nucleic acid. The meaning of the term "metalation" in means of the invention is disclosed on page 7, last paragraph of the application as filed: "*The most straight forward binding approach is 'metalation'. This process refers to direct ('covalent') bonding between a metal atom and a site on the nucleic acid, [...]*"

Applicants submit that it is not clear from the descriptions by Pompe and Richter whether ionic interactions are involved in the binding of Pd^{2+} to DNA. They indicate that "metalation" is a likely process. They do not discuss the possibility of electrostatic binding to the phosphate backbone of DNA but there is no reason to exclude that possibility. In any case, as already noted, the "Pd acetate solution" is not really a solution of $Pd(CH_3COO)_2$.

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 25-47 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 and 24-35 of co-pending Application Serial No. 10/210,812 (the " '812 application") in view of Singh et al. Applicants disagree.

A finding of obviousness-type double patenting turns on whether the invention defined in a claim in the application in issue is an obvious variation of the invention defined in a claim of a prior patent. *See, e.g., In re Berg*, 46 U.S.P.Q.2d, 1226 (Fed. Cir. 1998). In order for an obviousness-type double patenting rejection to stand, the Examiner must show that the claims in this application are obvious **based solely on the claims in the prior patent**; the disclosure in the prior patent can not be used as prior art.

When comparing the claims of the '812 application to the claims of the instant application, Applicants submit that the Examiner's provisional double patenting rejection is improper. For example, there is no teaching in the claims of the '812 application of removing non-conjugated metal complexes and/or non-conjugated by-products. Further, there is no motivation in the claims of the '812 application to combine its teachings with that of Singh in order to obtain the claimed invention. Applicants submit that the requisite suggestion and motivation are absent from the claims of the '812 application and the obviousness-type double patenting rejection must fail as a matter of law.

Consequently, reconsideration and withdrawal of the provisional obviousness-type double patenting rejection are respectfully requested.

V. DEPENDENT CLAIMS

The other claims in this application are each dependent on one of the independent claims discussed above and are therefore believed patentable for at least the same reasons. Since each dependent claim is also deemed to define an additional aspect of the invention, however, the individual reconsideration of the patentability of each on its own merits is respectfully requested.

CONCLUSION

In the event the Examiner disagrees with any of statements appearing above with respect to the disclosure in the cited reference, or references, it is respectfully requested that the Examiner specifically indicate the portion, or portions, of the reference, or references, providing the basis for a contrary view.

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In view of the foregoing amendments and remarks, it is believed that all of the claims in this application are patentable and Applicants respectfully request early passage to issue of the present application.

Respectfully submitted,
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